BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

REMARKS

Request for Continued Examination of the application in light of the amendment and remarks herein set forth is respectfully requested.

Applicant wishes to thank Examiner McKelvey for the courtesy extended to their representatives during the personal interviews of December 5, 2003 and February 20, 2004. The Interview Summary forms (PTOL-413) summarize the discussions held at the personal interviews. The present Amendment includes the substance of the examiner interview of February 20, 2004.

Applicant has replaced the abstract of the instant invention in order to better describe the invention as required under 37 C.F.R. § 1.72(a). The abstract has been rewritten to describe the invention as it is now claimed. No new matter has been added.

Applicant has taken this opportunity to correct several errors in the original specification. In the references section under "other publications," the citation of the La Thangue reference is corrected. The proper citation is found at column 12, line 28. At column 7, line 17 the phrase "see stippled segments" is moved closer to the phrase it modifies. The misspelling of steric is corrected at column 7, line 39. The proper moiety, as found in the context of the cited reference, of the receptor-ligand pair, is used at column 9, line 5. Table II should be cited when introduced in the text at column 10, line 50. Several subsequent citations of "Table II," or "Table 2" are changed to "Table III," since they refer to the subject matter of Table III.

SUBSTANCE OF EXAMINER INTERVIEW OF FEBRUARY 20, 2004

During the personal interview of February 20, 2004, Applicant pointed out mistakes by their former representative involving sentence structure and logical errors found during a review

of the record. Applicant reviewed the language found in the second paragraph of the remarks section on page 4 of paper 16:

> By this *Second Supplemental Amendment*, Applicant has canceled Claims 15-21 directed to an embodiment supplemental to original Claims 1-14 where the embodiment is a transfection vector that consists of an NLS only.

Applicant remarked that the statement above is ambiguous because it could describe Claims 15-21 *or* Claims 1-14 as limited to "an NLS only." It is a syntactical error to place the phase "where the embodiment is a transfection vector that consists of an NLS only" after "original Claims 1-14." The Examiner agreed the sentence was ambiguous and that Claims 1-14 are not limited to consists of an NLS only.

Applicant reviewed the statements of paper 16. The statements pointed to appear to be part of a summary of the personal interview of January 22, 2001. Applicant pointed out that aggregating the statements in the Table to define Claim 1 was illogical. For example, a claim cannot be both "6-50 amino acids" in length *and* "6-25 amino acids" in length. That is, a single claim element can not be defined by differing scopes. The claim scope "taken from the group consisting of G, A, L and I" (glycine, alanine, leucine and isoleucine) has a different scope than "neutral small amino acids without any bulky hydrophobic or ionic side chains." Applicant asserts Claim 1 is defined by the unambiguous "plain language" of the claim and does not require importation of limitations from the specification. Applicant does not disavow claim scope based on the arguments of paper 16.

Applicant discussed the Examiner's point in paper 28, regarding the lack of distinction in the specification between hinges and spacers. Applying this argument means that the inventor did not provide a definition in the specification that would import limitations into or change the plain meaning of the term "hinge" in Claim 1, and if the specification of the instant application does not distinguish between or exclude either spacers or hinges, then the scope of Claim 1 must

include those linkers of neutral amino acids[1] called "hinges" as well as those linkers of neutral amino acids called "spacers."[2] Applicant pointed out the text of M.P.E.P § 2111.01 for deliberation:

> 2111.01 Plain Meaning [R-1]
>
> THE WORDS OF A CLAIM MUST BE GIVEN THEIR "PLAIN MEANING" UNLESS THEY ARE DEFINED IN THE SPECIFICATION
>
> While the ** claims of issued patents are interpreted in light of the specification, prosecution history, prior art and other claims, this is not the mode of claim interpretation to be applied during examination. During examination, the claims must be interpreted as broadly as their terms reasonably allow. This means that the words of the claim must be given their plain meaning unless applicant has provided a clear definition in the specification. In re Zletz, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) [...]

A definition was reviewed that defined the term hinge as synonymous with a connector.[3] M.P.E.P § 2111.01 requires a clear definition[4] in the specification before changing the meaning of claim language from its "plain meaning."

Applicant pointed out the Examiner's statements on page 6 of paper 28 that discuss the phrase "separated by a hinge to prevent steric interference between the two domains." The Examiner agreed the phrase "separated by a hinge to prevent steric interference" could be

---

[1] Neutral amino acids covered by the claim scope of claim 1 from Fig. 2-2, p. 21, Essentials of Molecular Biology (4th Ed.) Malacinski, Jones and Barlett, Eds. (2003).

[2] For example, the "SGGGGG" of the specification and the previously cited examples (*e.g.* "GGGGYG" and "(GGGGGGGGGGGGGSGG") fall within the scope of claim 1 whether these linkers are called spacers or hinges.

[3] Hinge NOUNS 1. joint, join, joining, junction, union, connection, link, connecting link, coupling, accouplement; cinch, embrace; pivot [...] Roget A to Z (1994).

[4] Applicant notes Examiner's comment in paper 28 that "the instant application defines a hinge region separating the DNA binding domain and NLS peptide as a 'hinge region of neutral amino acid, to minimize stearic interference between the two domains. For this purpose, the hinge region ranges in length from about six to twenty-five amino acids, and contains a stretch of neutral small amino acids without any bulky hydrophobic or ionic side chains'." Examiner's sentences refer to one possible embodiment (having about six to twenty-five amino acids at column 7, line 41). Other embodiments of different scope are also presented (having about six to fifty amino acids at column 3). Thus, it is inappropriate to pick ne f the examples to limit the plain meaning of Claim 1 which does not have a numerical limitation in hinge region length.

interpreted as separated along the length of the polypeptide. That is, the hinge separates in terms of primary sequence, *i.e.* the hinge connects the two other elements. Applicant pointed out that the hinge is between the two domains and the phrase could well mean the structure of the hinge does not sterically interfere with the two domains moving about or coming together. The Examiner agreed that there exists ambiguity in the wording and that the wording could cover both linkers of neutral amino acids called "hinges" and "spacers." Applicant pointed out ambiguous phrases cannot be used to limit the plain meaning of the language of Claim 1. The language of Claim 1 is that of a structure and should not have functional limitations imported into it from the specification.

Applicant pointed to the wording made by their prior representative starting on page 6 in paper 16, :

> "Consequently, there would be stearic [sic] interference with the domains, diminishing their ability to serve their purpose (for which the NLS domain is self-explanatory and for the BAA domain is to link electrostatically to a DNA)."

Applicant would like to make it clear that "BAA" is not the language of Claim 1. Further, the elements of the claims are not limited by "purpose." That is, the "purpose" of an NLS sequence would not exclude it from binding to DNA and/or serving as a polymeric chain of basic amino acid residues.

During the interview, Examiner agreed that many NLS moieties, *e.g.* the SV40 T Antigen, "PKKKRKV," could serve as a polymeric chain of basic amino acid residues in the instant invention. Additionally, in order to show that one of ordinary skill in the art realized NLS sequences could bind DNA, Applicant pointed to the language of U.S. Pat. No. 5,972,900 starting at column 9, line 48:

> In some instances, the nucleic acid binding moiety, which maintains the nucleic acid in the compacted state, may also serve as a targeting agent. Polymers of

positively charged amino acids are known to act as nuclear localization signals (NLS) in many nuclear proteins.

The Examiner agreed that the SV40 T Antigen sequence could serve as a polymeric chain of basic amino acid residues in the instant invention and requested the patent be included in the accompanying IDS. Applicant discussed the history of claims previously presented in this application. These claims, wherein the electrostatically linked synthetic polypeptide consists of an NLS peptide, were suggested in order to overcome the Szoka reference in the examiner interview of July 10, 2000 (see paper 6½). Applicant was informed by prior representation that all of the rejections of record were traversed by the arguments of the Amendment filed September 7, 2000 (paper 11a). Applicant may submit the previously presented claims in a future amendment.

Several other topics were discussed in the examiner interview that are mentioned, with attribution to the Examiner, in the sections below.

REJECTIONS UNDER 35 U.S.C. § 102

Claims 2, 5, 8, 10-11 and 14 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Woo et al., ("Woo") (U.S. Patent No. 5,994,109), and alternatively, under U.S.C. § 102(a) as being anticipated Smith et al. ("Smith") (WO 93/18759). Applicant respectfully traverses and requests withdrawal of the rejection based on the arguments and declaration submitted herewith.

The Examiner allowed Claims 1, 3, 4, 6 and 7 in the Office Action of September 10, 2003 because Applicant's Rule 131 declaration of June 16, 2003 "provided an adequate basis for inferring that the invention has generic applicability as drawn to Claims 1, 3-4, and 6-7, [...]." Applicant agreed during the personal interview of December 5, 2003 that the claims can be so allowed under the second part of paragraph three in M.P.E.P § 715.03(B).

The Examiner rejected Claims 2, 5, and 8-14 based on an insufficiency of proof of that Applicant's prior possession carried with it sufficient "generic applicability" as drawn to the rejected claims. Applicant respectfully traverses.

Applicant asserts proof of prior possession is not limited to a demonstration of "generic applicability" as drawn to the rejected claims. The Examiner's rejection of September 10, 2003 stated:

> "The declaration and evidence filed on 6/16/03 does not show a reduction to practice of the claimed invention drawn to having the following limitations: polymeric chain being within the particular range of 10 to 50 residues (Claim 2), that the hinge region is between 6 and 50 amino acid residues (Claim 5), that the transfection vector further comprises a cell type-specific ligand molecule (Claim 8), or that the DNA structural sequence is specifically one selected from certain specific types of sequences (Claims 9-14). The specific species described in the declaration and supporting evidence does not provide an adequate basis for inferring that the invention has applicability regarding the additional limitations as claimed because there is nothing about the species that would lead one to infer the claimed invention drawn to the additional limitations of Claims 2, 5, and 8-14." (Page 4 bridging page 5.)

An examination of cases cited in M.P.E.P § 715.03 shows that an examiner cannot limit Applicant to a showing of generic applicability for each claim. The court in *Hostettler* reviewed an examiner's requirement (*see*: p. 564, upper right) that an applicant show the exact species or generic applicability under M.P.E.P § 715.03. (*In re Hostettler*, 356 F.2d 562, 148 USPQ 514 (CCPA 1966).) The court reversed, allowing the applicant to antedate a reference by showing prior possession of the basic invention earlier than the effective reference date:

> Rule 131 requires applicant to make oath to facts showing a completion "of the invention." That requirement does not mean affiant must show a reduction to practice of every embodiment of the invention. Nor is that requirement co-extensive with the amount of disclosure necessary to support a claim under 35 U.S.C. § 112. (*In re Hostettler*, 356 F.2d 562, 565; 148 USPQ 514 (CCPA 1966).)
>
> Certainly appellants should not be required to submit facts under Rule 131 showing that they reduced to practice that which is obvious in addition to those

facts offered as showing a completion of the invention, for the purposes of antedating a reference. (*Id.* at 566-67).

Applicant points to the MPEP §§ 715.02 and 715.03 for support of their argument. The law as stated in these sections does not require that an applicant's showing "lead one to infer the claimed invention drawn to the additional limitations" in order to antedate a reference. Rather, sections 715.02 and 715.03 detail the requirements for direct and indirect antedating and the circumstances that determine how much of the claimed invention must be represented by the showing. The sufficiency of the showing depends upon factors such as the nature of references, the type of rejection, the extent to which the claimed invention is shown in the reference, and what is known and obvious to one of ordinary skill in the art. During the personal interview of December 5, 2003, the Examiner was persuaded by Applicant's arguments and agreed that Applicant may directly or indirectly antedate the cited references to overcome the remaining rejected claims. Below, in the section entitled "Antedating Basis For Rejections under 35 U.S.C. §§ 102 and 103," Applicant addresses how their Rule 131 showing of June 16, 2003 meets the requirements to antedate the cited references for each claim rejected in Examiner's rejection of September 10, 2003.

REJECTIONS UNDER 35 U.S.C. § 103

Claims 2, 5, 8-11 and 14 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over either Woo or Smith in view of Short ("Short") (U.S. Patent No. 5,589,392). Applicant respectfully traverses and requests withdrawal of the rejection based on the arguments and declaration submitted herewith.

Short teaches the use of a DNA sequence for regulating gene expression employing a nucleic acid molecule that encodes a nuclear transport signal peptide linked by a peptide bond to an inducible repressor peptide. Once inside the cell nucleus, the DNA sequence of the invention

is expressed. Thus, the resulting polypeptide (NLS joined directly to a repressor which blocks transcription) is always inside the cell nucleus, able to regulate gene expression under the control of an inducer molecule. The inducer molecule can then be added to the cell medium for uptake by the cell. Once inside the cell, the inducer molecule binds the repressor such that the repressor dissociates from the operator, allowing gene expression within the cell.

Short does not teach associating an NLS-containing peptide electrostatically to a structural DNA sequence and then introducing the complex into a cell. There is no reason to combine the teachings of Short with Woo or Smith for use in a transfection vector. There is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings as required in M.P.E.P. § 2143. Applicant respectfully asserts that the rejection under 35 U.S.C. § 103(a) is improper.

Claims 2, 5, 8, and 10-14 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over either Woo or Smith in view of Gorman ("Gorman") (U.S. Patent No. 5,024,939). Applicant respectfully traverses and requests withdrawal of the rejection based on the arguments and declaration submitted herewith.

Gorman teaches use of a trans-activating protein comprising a stabilizing sequence downstream of a promoter and a polyadenylation sequence downstream of which is a transcription termination site for transient production of a desired heterologous protein.

Gorman does not teach associating an NLS-containing peptide electrostatically to a structural DNA sequence and then introducing the complex into a cell. There is no reason to combine the teachings of Gorman with Woo or Smith for use in a transfection vector. There is no suggestion or motivation, either in the references themselves or in the knowledge generally

available to one of ordinary skill in the art, to modify the reference or to combine reference teachings as required in M.P.E.P. § 2143. Applicant respectfully asserts that the rejection under 35 U.S.C. § 103(a) is improper.

Claims 2, 5, 8-11 and 14 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over either Woo or Smith in view of Short. Claims 2, 5, 8, and 10-14 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over either Woo or Smith in view of Gorman. Applicant asserts these rejections should be withdrawn in view of the arguments presented above. Specifically, as to Claims 2, 5, and 8 Applicant asserts that Woo and Smith are removed as references because they have been antedated using Applicant's Rule 131 showing of June 16, 2003. As to the remaining claims, Applicant submits that the attached declaration showing additional proof of prior possession of the subject matter of Claims 9-14 removes the Woo and Smith references. Since neither the Short reference nor the Gorman reference teaches the invention of the instant application, the rejection under 35 U.S.C. § 103(a) of the claims should be withdrawn.

ANTEDATING BASIS FOR REJECTIONS UNDER 35 U.S.C. §§ 102 and 103

Claim 2

Claim 2 recites the vector of Claim 1 (*i.e.*, having a polymeric chain of basic amino acid residues), wherein said polymeric chain is comprised of between 10 and 50 residues. Examiner's rejection of December 17, 2002 asserts that Claim 2 is anticipated by the Woo or Smith references and is obvious in light of these references in view of either Short (page 7) or Gorman (page 11). Applicant respectfully traverses the rejection of Claim 2. The rejection does not indicate where the limitations of Claim 2 of the instant application can be found in Woo, Smith, Short, or Gorman as required. One of ordinary skill in the art would know that a polymeric chain

of basic amino acid residues can have (as in claim 1 in the instant application, which does not have a numerical limitation) as few as one basic amino acid in the polymeric chain. But the specific limitation of claim 2 requires a polymeric chain of "between 10 and 50 residues." That range of 10 to 50 residues is not specifically stated in the Woo, Smith, Short, or Gorman references. Additionally, applicant points to the following paragraphs from the M.P.E.P.:

> [W]here the examiner, in rejecting a claim under 35 U.S.C. 103, has treated a claim limitation as being an obvious feature or modification of the disclosure of the reference(s) relied upon, without citation of a reference which teaches such feature or modification, a 37 CFR 1.131 affidavit or declaration may be sufficient to overcome the rejection even if it does not show such feature or modification. (MPEP § 715.02, paragraph 1)

> [A]pplicant's possession of what is shown carries with it possession of variations and adaptations which would have been obvious, at the same time, to one of ordinary skill in the art. (MPEP § 715.02, paragraph 3)

> Proof of prior completion of a species different from the reference species will be sufficient to overcome a reference indirectly under 37 CFR 1.131 if the reference species would have been obvious in view of the species shown to have been made by the applicant. In re Clarke, 356 F.2d 987, 148 USPQ 665 (CCPA 1966); In re Plumb, 470 F.2d 1403, 176 USPQ 323 (CCPA 1973); In re Hostettler, 356 F.2d 562, 148 USPQ 514 (CCPA 1966). (MPEP § 715.03(B), paragraph 3)

Without acquiescing to the rejection of Claim 2, and in order to expedite the instant application, Applicant shall offer a reference, as suggested by the Examiner in the December 5, 2003 personal interview. The reference is offered as additional evidence to be considered in the Applicant's antedating of the Woo and Smith references in regards to Claim 2 of the instant application. The reference is offered only to provide additional evidence regarding polymeric chains of basic amino acids residues, without any representation that the reference narrows the scope of the instant application.

Hancock et al., U.S. Patent No. 5,593,866, (a continuation-in-part of application Ser. No. 07/933,492, filed August 21, 1992) concerns a cationic peptide having anti-microbial activity. The cationic peptide is described in the specification as being from about 5 to about 50 amino

acids in length and preferably from about 15 to about 35 amino acids in length. Claim 1 claims a method producing a cationic peptide of unspecified length. Claim 3 claims the method of Claim 1, wherein the cationic peptide is from about 5 to about 50 amino acids.

The suitability of the reference was discussed with the Examiner in the personal interview of February 20, 2004. Applicant hereby submits the Hancock reference as additional evidence to be considered in the Applicant's antedating of the Woo and Smith references by Applicant's Rule 131 declaration of June 16, 2003.

Claim 5

Claim 5 recites the vector of Claim 1 (*i.e.*, having a hinge region of neutral amino acids), wherein said hinge region is comprised of between 6 and 50 amino acid residues. The Examiner's rejection of December 17, 2002 asserts that Claim 5 is anticipated by the Woo or Smith references and is obvious in light of these references in view of either Short (page 7) or Gorman (page 11). Applicant respectfully traverses the rejection of Claim 5. Applicant asserts the specific limitation of "between 6 and 50 residues" is not stated in the Woo, Smith, Short, or Gorman references. Additionally, applicant points to the following paragraphs from the M.P.E.P.:

> [W]here the examiner, in rejecting a claim under 35 U.S.C. 103, has treated a claim limitation as being an obvious feature or modification of the disclosure of the reference(s) relied upon, without citation of a reference which teaches such feature or modification, a 37 CFR 1.131 affidavit or declaration may be sufficient to overcome the rejection even if it does not show such feature or modification. (MPEP § 715.02, paragraph 1)
>
> Such evidence is sufficient because applicant's possession of what is shown carries with it possession of variations and adaptations which would have been obvious, at the same time, to one of ordinary skill in the art. (MPEP § 715.02, paragraph 3)
>
> Proof of prior completion of a species different from the reference species will be sufficient to overcome a reference indirectly under 37 CFR 1.131 if the reference

> species would have been obvious in view of the species shown to have been made by the applicant. In re Clarke, 356 F.2d 987, 148 USPQ 665 (CCPA 1966); In re Plumb, 470 F.2d 1403, 176 USPQ 323 (CCPA 1973); In re Hostettler, 356 F.2d 562, 148 USPQ 514 (CCPA 1966). (MPEP § 715.03(B), paragraph 3)

Without acquiescing to the rejection of Claim 5, and in order to expedite the instant application, Applicant shall offer a reference, as suggested by the Examiner in the December 5, 2003 personal interview. The reference is offered as additional evidence to be considered in the Applicant's antedating of the Woo and Smith references in regards to Claim 2 of the instant application. The reference is merely offered to provide additional evidence regarding peptide linkers of about between 6 and 50 residues in length, without any representation that it narrows the scope of the instant application.

Goodwin et al., U.S. Patent No. 5,674,704 (a continuation-in-part of application Ser. No. 08/060,843, filed May 7, 1993), concerns a cytokine polypeptide that is able to bind to a human cell surface receptor. In one embodiment, multiple copies of the cytokine can be connected using peptide linkers. Among the peptide linkers that may be employed are amino acid chains that are from 5 to 100 amino acids in length, preferably comprising amino acids selected from the group consisting of glycine, asparagine, serine, threonine, and alanine. More specifically, the specification describes the use of $Gly_4SerGly_5Ser$ (11 amino acids in length) and $(Gly_4Ser)_n$, where n ranges from 4-12 (20 to 60 amino acids in length).

In addition to the above examples of linkers of varied length, Applicant offers two additional examples that fall within the scope of Applicant's claims from the National Center for Biotechnology Information Center (NCBI) database. First, splicing factor SC35 (SFR2_HUMAN), accession #Q01130, contains a six-residue hinge from residue 111 to 116

(GGGGYG). Second, Seed Chitinase A (CHIA_MAIZE), accession #P29022 contains a 17-residue hinge from residue 61 to 77 (GGGGGGGGGGGGGGSGG).[5]

Applicant hereby submits the references above as additional evidence to be considered in the Applicant's indirect antedating of the Woo and Smith references by Applicant's Rule 131 declaration of June 16, 2003.

Claim 8

Claim 8 recites the vector of Claim 1 further comprising (D) a cell type-specific ligand molecule. Applicant respectfully asserts that the declaration of June 16, 2003 shows all that is required since the Office Action of December 17, 2002 rejected Claim 8 as obvious over the cited references:

> Even if applicant's 37 CFR 1.131 affidavit is not fully commensurate with the rejected claim, the applicant can still overcome the rejection by showing that the differences between the claimed invention and the showing under 37 CFR 1.131 would have been obvious to one of ordinary skill in the art, in view of applicant's 37 CFR 1.131 evidence, prior to the effective date of the reference(s) or the activity. Such evidence is sufficient because applicant's possession of what is shown carries with it possession of variations and adaptations which would have been obvious, at the same time, to one of ordinary skill in the art. (M.P.E.P. § 715.02, paragraph 3, underline emphasis added)

Applying M.P.E.P. § 715.02, Woo states at column 2, line 41, "Receptor-mediated endocytosis is a selective mechanism enabling cells to ingest large amounts of specific ligands without taking in correspondingly large amounts of extra-cellular fluid." Woo provides five references that show attachment of ligands to target DNA to cells. In column 2, line 60:

> Taking advantage of receptor-mediated endocytosis, the asialoglycoprotein receptor has been used in targeting DNA to HepG2 cells in vitro and liver cells in vivo. Wu and Wu, J. Biol. Chem., Vol. 262, pp. 4429-4432 (1987); Wu and Wu,

[5] To review this information, go to http://www.ncbi.nlm.nih.gov/pubmed select "protein" in the field labeled "search" and enter the accession number in the field labeled "for" (*e.g.* enter P29022 or Q01130). Search for "hinge" using your browser on the resulting page.

> Bio., Vol. 27, pp. 887-892 (1988); Wu et al., J. Biol. Chem., Vol. 263, pp. 14621-14624 (1988); Wu et al., J. Biol. Chem., Vol. 264, pp. 16985-16987 (1989); Wu et al., J. Biol. Chem., Vol. 266, pp. 14338-14342 (1991). These studies used asialoorosomucoid covalently linked to polylysine with water soluble carbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide or with 3'(2'pyridyldithio)propionic acid n-hydroxysuccinimide ester. Polylysine in the studies above bound DNA through ionic interaction. The DNA was ingested by endocytosis. (Woo '109 column 2, line 60 to column 3, line 6.)

Additionally, Applicant points to several references in the instant application that teach protocols that employ cell-specific ligands. At column 8, line 65, Applicant cites Michael, S. I., *et al.*, J. Biol. Chem. 268: 6866 (1993) for use with the instant invention. Michael teaches the use of a cell-specific ligand and adenovirus to exploit the receptor-mediated entocytosis pathway. Additional protocols employing cell-specific ligands are found in the instant specification.

In order to expedite the instant application, Applicant was asked in the December 5, 2003 personal interview to offer a reference describing use of a cell type-specific ligand molecule prior to the instant invention. Applicant hereby offers the above references as additional evidence of the use of a cell type-specific ligand molecule in the art, prior to the effective date of the reference. Said references, taken with the clear wording of M.P.E.P. § 715.02, paragraph 3, allows the Applicant to overcome the rejection without the need to offer evidence of prior reduction to practice of the instant invention with a cell type-specific ligand molecule attached.

Claims 9-11

Claims 9-11 of the instant application are as follows:

> 9. The transfection vector of Claim 1, wherein said DNA structural sequence comprises (a) a segment coding for SV40 large T antigen or polyoma large T antigen and (b) a transcription factor gene.
>
> 10. A vector according to Claim 1, wherein said DNA structural sequence comprises an oncogene.

> 11. A vector according to Claim 10, wherein said oncogene is selected from the group consisting of SV40 large T antigen, polyoma large T antigen, adenovirus E1A, adenovirus E1B, v-fms, BC12, myc, and ras.

Examiner's rejection of December 17, 2002 comments that the DNA structural sequences of Claims 9-11 are not specifically taught by Woo or Smith (page 9 bridging 10). It is the Examiner's position that the DNA structural sequences of Claim 9-11 are well known in the art and would have been obvious to use (*Ibid.*, page 11, paragraph 2). Based on the Examiner's position, Applicant asserts antedating Claims 9 and 11 is not required under MPEP § 715.02 paragraph 1, which states that a declaration need not show the limitation if that limitation is not present in the reference. In addition, MPEP § 715.03 (B) paragraph 4 states that the applicant need not show possession of any more than what the reference shows. Also, possession of what is shown in the 1.131 carries with it possession of variations and adaptations that would have been obvious. (MPEP § 715.02 paragraph 3).

Accordingly, the rejection under 35 U.S.C. §§ 102 and 103 of Claims 9-14 should be withdrawn based on Applicant's June 16, 2003 Rule 131 affidavit.

Claim 12

Claim 12 recites the vector according to Claim 1 with the added limitation:

> "wherein said DNA structural sequence comprises a DNA sequence selected from the group consisting of a dihydrofolate reductase gens (DHFR), a thymidine kinase gens, a thymidylate synthetase gene a DRTF1/E2F transcription factor-encoding DNA sequence, and an E2F transcription factor-encoding DNA sequence."

In the Office Action of December 17, 2002, the Examiner combined Gorman with the Woo and Smith references to reject this claim as obvious. Applicant directs the Examiner to the following paragraph of MPEP § 715.02:

> Where a claim has been rejected under 35 U.S.C. 103 based on Reference A in view of Reference B, with the effective date of secondary Reference B being earlier than that of Reference A, the applicant can rely on the teachings of Reference B to show that the differences between what is shown in his or her 37 CFR 1.131 affidavit or declaration and the claimed invention would have been obvious to one of ordinary skill in the art prior to the date of Reference A.

The Gorman issue date is prior to the Woo and Smith reference dates and thus can be used by the Applicant to antedate the primary references of Woo and Smith.

Claims 13 and 14

Claims 13 and 14 are as follows:

> 13. A process for producing a transformed mammalian cell line, comprising the step of transfecting a mammalian cell with a vector according to Claim 1, wherein said DNA structural sequence comprises a DNA sequence selected from the group consisting of a dihydrofolate reductase gene (DHFR), a thymidine kinase gene, a thymidylate synthetase gene a DRTF1/E2F transcription factor-encoding DNA sequence, and an E2F transcription factor-encoding DNA sequence.
>
> 14. A process for producing a transformed mammalian cell line, comprising the step of transfecting a mammalian cell with a vector according to Claim 1, wherein said DNA structural sequence comprises an oncogene.

Both claims are directed to "a process for producing a transformed mammalian cell line." The Office Action of December 17, 2002 rejects these claims as obvious and anticipated (pages 7 and 11 of paper 28), but does not inform Applicant where the limitations of Claims 13 and 14 are present in the references. Because the "process for producing a transformed mammalian cell line" is not stated in the Woo, Smith, Short, or Gorman references, the Applicant traverses the §§ 102 and 103 rejection of Claims 13 and 14.

Additionally, Applicant cites the following sentence from MPEP § 715.02 paragraph 1:

> where the examiner, in rejecting a claim under 35 U.S.C. 103, has treated a claim limitation as being an obvious feature or modification of the disclosure of the reference(s) relied upon, without citation of a reference which teaches such

feature or modification, a 37 CFR 1.131 affidavit or declaration may be sufficient to overcome the rejection even if it does not show such feature or modification.

Thus, Applicant asserts that the June 16, 2003 Rule 131 affidavit should be sufficient to antedate the references of record.

RULE 131 AFFIDAVIT SUPPORTING PRIOR POSSESSION OF CLAIMS 9-14

In order to expedite the allowance of the instant application, without acquiescing to the rejections of record, Applicant offered to submit an additional Rule 131 affidavit during the personal interview of December 5, 2003. Upon review of the evidence, the Examiner agreed that a second Rule 131 affidavit would be appropriate to show additional evidence of prior possession of the subject matter in Claims 9-14 prior to the Woo or Smith references. Applicant hereby attaches said Rule 131 affidavit showing additional evidence of prior possession of the subject matter in Claims 9-14 prior to the effective date of the Woo or Smith references. Accordingly, Applicant respectfully asserts the rejection under 35 U.S.C. §§ 102 and 103 of Claims 9-14 should be withdrawn.

CONCLUSION

Applicant respectfully submits that the claims now stand ready and in condition for allowance. Early consideration of the above amendments and remarks and of the Declaration attached is respectfully requested.

By: Kellie L. Carden
Kellie L. Carden
Registration No. 52,696

Patton Boggs, LLP
8484 Westpark Drive
9th Floor
McLean, Virginia 22102
(703) 744-7919 (direct)
(703) 744-8001 (facsimile)
kcarden@pattonboggs.com

ASMC Tx at p3 in Suspension

[redacted] ASmc - for one plate dish at p3. Trypsinize. Spin down cells. Rinse 1x ~ 1x HBS. Add 200λ of 1x trypsin - 3 min RT. Spin. Aspirate supernatant Completely. Add DNA in 100 λ as follows:

	LLT	LE2F-1	Expression-1 Co-plasmid	1x HBS	H2O	Cells	DNA
A	5	5	6λ	25λ	59λ	ASMC-1	100λ

Incubate at 37°C - 10 min. - Add 2ml 1x HBS - Spin. Plate cells in 1 plate - in SmGm - P3

Control - ASMC - in 1 p60 - P3

[redacted] Both Control and Txed cells look very similar - Confluent.

ASMC - Control - Split 1:10 - 1 p60 SmGm - P4

ASMC Txed Cell - Freeze 1 vial - Maintain 1:10 1 plate - SmGm Periodic med change.

[redacted] Control Cells - beginning to slow down. med. change.

ASMC - Txed - Good Growth - nearly Confluent

[redacted] ASmc - Split 1:10 - 1 plate SmGm - P5

[redacted] ASmc - med. change. Also to Control. Control cells nearly confluent - but look Stretched and flatter than txed cells

[redacted] ASmc - Control - Split 1:5 - 1 p60 - P5

ASmc Txed - med. change - P5

[redacted] ASmc - freeze 1 vial - P6. maintain 1:10 - 1 plate SmGm

[redacted] I think ASMC control will not grow any further

Definitely txed cells (LT + E2F-1) Can give rise to cells with extended life Compared to untransfected cells.

B

[redacted] ASmc - med. change - p6 SmGm

[redacted] ASmc - freeze 1 vial - P7 maintain 1:10 1 plate SmGm Periodic med. change + Continuous maintenance

[redacted] ASmc - frozen at p5; Control cells did not Grow beyond p5. Even at p5 cells are morphologically Very different & Stretched out.

[redacted] ASmc - now in p12 - Seems to slow down a bit. These cells are definitely extended life cells but may not be Completely transformed cells.

T. V. Sajal

[redacted]

HUVEC Tx at p6 in 12 well plate

[redacted] HUVEC - Plated in 12 well plate the day before in EGM5 cells 80 % Confluent at time of Tx

HUV-1 - 5 x each of LTEx + LEIA + 0.3 x Cx in 300 λ

HUV-2 - 5 x each of LEIA + LEIB + 0.3 x Cx in 300 λ

	LTEx	LEIA	LEIB	Expression 0.05 mg/ml	1x HBS	H2O	Cells
1	10 λ	10 λ	-	6 λ	125	178	HUV-1
2	-	10 λ	10 λ	6 λ	125	178	HUV-2

C

Aspirate med. Add 1.0 ml 1x Hypo - 3 min RT. Aspirate. Add DNA in 300 λ - 4 min RT. Add 1.5 ml 5+ med. Aspirate. Add 2.0 ml EGM5

[redacted] Called Cells - Plate each in 1 plate - EGM5 - P7

[redacted] HUV-1 & HUV-2 both look similar - Nearly Aj. Confluent.

[redacted] HUV-1 + HUV-2 - freeze 1 vial each - P8

Split 1:10 1 plate each EGM5 - P8

[redacted] Looks like HUV-2 (EIA + EIB) not as good as HUV-1. Cells in HUV-2 appear to be more stretched out.

[redacted] HUV-1 - freeze 1 vial. maintain 1:10 1 plate - EGM5 P9

HUV-2 - med. Change P8

[redacted] HUV-2 - Nearly Confluent - Split 1:5 1 p60 - P9

[redacted] HUV-1 - Split 1:10 1 plate EGM5 - p10. Not of its cells freeze.

[redacted] HUV-2 - Doesn't look like it will grow too far Compared to HUV-1

LTEx + LEIA is a better Combination for transforming HUVEC cells Compared to EIA + EIB

[redacted] HUV-2 freeze 1 vial - Not maintained any more. p10

HUV-1 Still growing very well at p12

D

Test for markers - training.

IL-1 induction to ELAM-1 & VCAM-1 - Train

Continue to maintain HUV-1

[redacted] HUV-1 - Trained for both ELAM-1 & VCAM-1 - Good training even at p14. Now is p15

Thank you

[redacted]

[redacted] DMV at p4 Tx on 12 well plates

Cells thawed + plated in 4hr before Tx. Nearly 90% Confluent

DMV-021 – 2.5 × each LTRx + LEIA + 0.1 × Cx in 300λ
DMV-022 – 2.5 × each LLT + LEIA + 0.1 × Cx in 300λ

	LTRx	LLT	LEIA	Expression-1 (0.05 mg/ml)	1x HBS	H_2O	Cells
E 1	5λ	–	5λ	2λ	133	138	DMV-021
2	–	5λ	5λ	2λ	135	138	DMV-022

Aspirate med. Add 0.7 ml 1x Hyper – 4 min RT. Aspirate
Add DNA in 300λ – 4 min RT. Add 1.5 ml SF med. Aspirate
Add 1.5 ml EGMS

Comment: Cells looked fine after Tx.

[redacted] Cells Trypsinized and each plated in 1 p60 EGMS – P5
[redacted] Each transferred to one p60 EGMS rec – P6
[redacted] DMV-021 + DMV-022 Split 1:5 1 new each EGMS – P 2
[redacted] DMV-021 + DMV-022 Freeze 1 vial each.
Maintain 1:10 1 p60 each – EGMS – P8
[redacted] Split from 1:10 – 1 p60 each – P9
[redacted] Both DMV-021 + DMV-022 looks healthy.
Control untransfected cells – have detached out
∴ Both transforming genes Trx, LT, together with EIA
Can generate extended life cells.
F Can be immortalized also.
Continue to maintain the cells for several passages to determine exactly how long the cells can be taken
[redacted] DMV-021 + DMV-022 – Split 1:5 EGMS P10
[redacted] Freeze DMV-021 + DMV-022. Maintain 1:5 p11
[redacted] DMV-021 + DMV-022 – Split p12.

[redacted] Rem DMV-021 + DMV-022 – now in p14. Freeze 1 vial each
Maintain 1:5 p60 EGMS – P15
[redacted] DMV-021 in 1 p60 – Total cells from one confluent p60 dish B in 1.2×10^6 cells.
[redacted] DMV-022 in now in p17
Test Cell Applications Endothelial cells rec.
Both plated in CADMEC Growth med p17
1/2 of the cells maintained in EGMS

[redacted] Both DMV-021 + 022 grow well in either med.
Confirmed
[redacted]